REMARKS

1. Applicants hereby submit the following:

[ ] a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

[XX] an amendment to the paper copy of the "Sequence Listing" submitted on April 2, 2001, the amendment being in the form of substitute sheets;

[XX] the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;

[ ] pursuant to §1.821(e), reference is made to the computer readable form filed on , in USSN , which presents the identical Sequence information, the use of which is now requested, in lieu of submitting a new computer readable form; and/or

[ ] a substitute computer readable form to replace one found to be damaged or unreadable.

[XX] 2. The description has been amended to comply with §1.821(d).

3. The undersigned attorney or agent hereby states as follows:

(a) this submission is not believed to include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are believed to be the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is believed to be supported by the specification and is not believed to include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is believed to be identical to that originally filed [§1.825(d)].

4. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of

"Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free

sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph beginning at line 5 of page 21 has been amended as follows:

Specific examples of deletions comprise or essentially consist of residues 1 to 26, residues 1 to 23, and residues 1 to 20, respectively, of the fragment: Ala - Leu - Asp - Ala - Ala - Tyr - Cys - Phe - Arg - Asn - Val - Gln - Asp - Asn - Cys - Cys - Leu - Arg - Pro - Leu - Tyr - Ile - Asp - Phe - Lys - Arg - Asp - Leu - Gly (SEQ ID NO:1); i.e. fragments or compositions of fragments comprising either

The paragraph beginning at line 20 of page 21 has been amended as follows:

Additional examples of specific deletions comprise or essentially consist of residues 4 to 29, residues 7 to 29, and residues 10 to 29, respectively, of the fragment: Ala - Leu - Asp - Ala - Ala - Tyr - Cys - Phe - Arg - Asn - Val - Gln - Asp - Asn - Cys - Cys - Leu - Arg - Pro - Leu - Tyr - Ile - Asp - Phe - Lys - Arg - Asp - Leu - Gly (SEQ ID NO:1); i.e. fragments or compositions of fragments comprising either

The paragraphs beginning at line 18 of page 29 and ending at line 8 of page 30 have been amended as follows:

In another interesting embodiment of the present invention the fragment of TGF-β capable of eliciting an immunostimulating effect comprises the amino acid sequence:

X-A-Arg-B-Leu-Tyr-Ile-Asp-Phe-H-I-Asp-Leu-Gly-Trp-Lys (SEQ ID NO:3),

wherein X is Cys or a crosslinker moiety or a polypeptide that has at its C-terminus a Cys, and that, if greater than 15 residues, does not have the sequence of mature or precursor TGF-β at a homologous location in the mature or precursor TGF-β molecule; and

wherein A is Val or Leu; B is Pro or Gln; H is Arg or Lys; and I is Lys, Arg, or Gln; or a physiologically acceptable salt or ester thereof; with the proviso that the TGF-β fragment excludes (a) a full-length mature TGF-β molecule or precursor TGF-β molecule or deletion variants of mature or precursor TGF-β molecules in which from about 1 to 10 amino acid residues have been deleted, (b) a fragment of the sequency: Cys-Val-Arg-Gln-Leu-Tyr-Ile-Asp-Phe-Arg-Lys-Asp-Leu-Gly-Trp-Lys (SEQ ID NO:4), and (c) a fragment of the sequence: Arg-Asn-Leu-Glu-Glu-Asn-Cys-Cys-Val-Arg-Pro-Leu-Tyr-Ile-Asp-Phe-Arg-Gln-Asp-Leu (SEQ ID NO:5).

Preferred fragments are Cys-Leu-Arg-Pro-Leu-Tyr-Ile-Asp-Phe-Lys-Arg-Asp-Leu-Gly-Trp-Lys (SEQ ID NO: 2); Cys-A-Arg-B-Leu-Tyr-Ile-Asp-Phe-H-I-Asp-Leu-Gly-Trp-Lys (SEQ ID NO:6), and Cys-Val-Arg-B-Leu-Tyr-Ile-Asp-Phe-Arg-I-Asp-Leu-Gly-Trp-Lys (SEQ ID NO:7), wherein: B is Pro or Gln; and/or I is Lys or Gln; and A and H are as defined herein above. It is more preferred that B is Gln and I is Lys, and that B is Pro and I is Gln.

The paragraph beginning at line 32 of page 51 has been amended as follows:

In one embodiment of the present invention the immunogenic determinant is derived from a Parvovirus. Said immunogenic determinant could be naturally occurring or it could be synthesized in vitro. For example said immunogenic determinant could be a polypeptide, such as a polypetide comprising the amino acid sequence CDGAVQPDGGQPAVRNER (SEQ ID NO:8) or a derivative thereof. Another example of a preferred immunogenic determinant is recombinant *A. salmonicida* outer membrane protein (rAsOMP). rAsOMP could for example be produced in *E. coli* . Preferably, rAsOMP is used at a final purity of ~75%.

The paragraph beginning at line 15 of page 59 has been amended as follows:

(Abbreviations: PBS = Phosphate Buffered Saline; crude fraction = composition comprising TGF-29 at a purity of about 50%; Parv: Synthesised 18-mer parvo virus peptide derivate acetyl-CDGAVQPDGGQPAVRNER-amide (SEQ ID NO:8), purity more or about 95% (R831, ID-LELYSTAD, The Netherlands, ref: Langeveld J.P.M., Casal J.I., Osterhaus A.D.M.E., Corter E., de Swart R.,Vela C., Dalsgaard K., Puijk W.C., Schaaper W.M.M. and Meloen R.H. (1994). First peptide vaccine providing protection against viral infection in the target animal: Studies of canine parvovirus in dogs. J. Virology 68:4506-4513.)).

The paragraph beginning at line 31 of page 61 has been amended as follows:

(Abbreviations: Tris-HCl : Tris is a common trade name for a commercially (eg.Sigma) available buffer salt solution adjusted with H_20 and HCl to desired pH and molarity; purified TGF-29 = composition comprising TGF-29 at a purity of about 95%; Parv: Synthesised 18-mer parvo virus peptide derivate acetyl-CDGAVQPDGGQPAVRNER-amide (SEQ ID NO:8), purity more or about 95% (R831, ID-LELYSTAD, The Netherlands, ref: Langeveld J.P.M., Casal J.I., Osterhaus A.D.M.E., Corter E.,

de Swart R., Vela C., Dalsgaard K., Puijk W.C., Schaaper W.M.M. and Meloen R.H. (1994). First peptide vaccine providing protection against viral infection in the target animal: Studies of canine parvovirus in dogs. J. Virology 68:4506-4513)).

The paragraph beginning at line 19 of page 66 has been amended as follows:

(Abbreviations: Titermax adjuvant : Titermax Classical Adjuvant, Product no H4397, SIGMA-ALDRICH DENMARK A/S; Purified TGF-29 = composition comprising TGF-29 at a purity of about 95%; Parv: Synthesised 18-mer parvo virus peptide derivate acetyl-CDGAVQPDGGQPAVRNER-amide (SEQ ID NO:8), purity more or about 95% (R831, ID-LELYSTAD, The Netherlands, ref: Langeveld J.P.M., Casal J.I., Osterhaus A.D.M.E., Corter E., de Swart R., Vela C., Dalsgaard K., Puijk W.C., Schaaper W.M.M. and Meloen R.H. (1994). First peptide vaccine providing protection against viral infection in the target animal: Studies of canine parvovirus in dogs. J. Virology 68: 4506-4513)).